

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 December 2007 (27.12.2007)

PCT

(10) International Publication Number
WO 2007/148070 A1

(51) International Patent Classification:

C07D 403/04 (2006.01) A61P 35/04 (2006.01)
A61P 35/02 (2006.01) A61K 31/506 (2006.01)

(74) Agent: GLOBAL INTELLECTUAL PROPERTY; AstraZeneca AB, S-151 85 Södertälje (SE).

(21) International Application Number:

PCT/GB2007/002279

(22) International Filing Date: 20 June 2007 (20.06.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/805,353 21 June 2006 (21.06.2006) US

(71) Applicant (for all designated States except MG, US): ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(71) Applicant (for MG only): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): JONES, Clifford [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). MATUSIAK, Zbigniew, Stanley [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

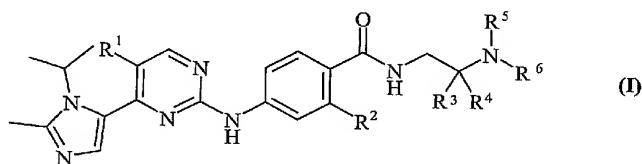
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CHEMICAL COMPOUNDS



(57) Abstract: Compounds of formula (I) which possess cell cycle inhibitory activity are described.



WO 2007/148070 A1

CHEMICAL COMPOUNDS

The invention relates to pyrimidine derivatives, or pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof, which possess cell-cycle inhibitory activity and are accordingly useful for their anti-cell-proliferation (such as anti-cancer) activity and are therefore useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cell-proliferation effect in a warm-blooded animal such as man.

The cell cycle is fundamental to the survival, regulation and proliferation of cells and is highly regulated to ensure that each step progresses in a timely and orderly manner. The progression of cells through the cell cycle arises from the sequential activation and de-activation of several members of the cyclin-dependent kinase (CDK) family. The activation of CDKs is dependent on their interaction with a family of intracellular proteins called cyclins. Cyclins bind to CDKs and this association is essential for CDK activity within the cell. Different cyclins are expressed and degraded at different points in the cell cycle to ensure that activation and inactivation of CDKs occurs in the correct order for progression through the cell cycle.

Moreover, CDKs appear to be downstream of a number of oncogene signalling pathways. Deregulation of CDK activity by upregulation of cyclins and/or deletion of endogenous inhibitors appears to be an important axis between mitogenic signalling pathways and proliferation of tumour cells.

Accordingly it has been recognised that an inhibitor of cell cycle kinases, particularly inhibitors of CDK1, CDK2, CDK4 and CDK6 (which operate at the G2/M, G1/S-S-G2/M and G1-S phases respectively) should be of value as an active inhibitor of cell proliferation, such as growth of mammalian cancer cells.

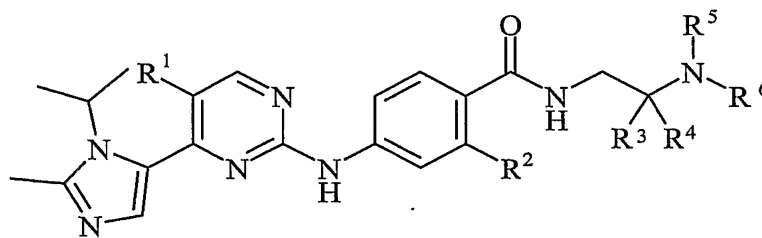
Tumour cells are also thought to be highly dependent on the continual transcriptional activity of RNA polymerase II to maintain appropriate levels of anti-apoptotic proteins and ensure tumour cell survival. CDK1, CDK7, CDK8 and CDK9 in particular are known to regulate the activity of RNA polymerase II through phosphorylation of the C-terminal domain of the protein. Thus, the inhibition of RNA polymerase II activity through inhibitors of these CDKs may contribute to a pro-apoptotic effect in tumour cells.

- 2 -

The inhibition of cell cycle kinases is expected to be of value in the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

WO 02/20512, WO 03/076435, WO 03/076436, WO 03/076434, WO 03/076433 and WO 04/101549 describe certain 2-anilino-4-imidazolylpyrimidine derivatives that inhibit the effect of cell cycle kinases. The present invention is based on the discovery that a novel group of compounds inhibit the effects of CDK2, and thus possess anti-cell-proliferation properties.

Accordingly, the present invention provides a compound of formula (I):



(I)

wherein:

R^1 is hydrogen, halo or cyano;

R^2 is hydrogen or halo;

R^3 , R^4 , R^5 and R^6 are independently selected from hydrogen and methyl optionally substituted by hydroxy;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

The term "halo" refers to fluoro, chloro, bromo and iodo.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or

- 3 -

tris-(2-hydroxyethyl)amine.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess CDK inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess CDK inhibitory activity.

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

R¹ is hydrogen.

R¹ is halo.

R¹ is fluoro.

- 4 -

R¹ is chloro.

R¹ is hydrogen, fluoro or chloro.

R¹ is hydrogen, fluoro, chloro or cyano.

R² is hydrogen.

5 R² is halo.

R² is fluoro.

R² is chloro.

R² is hydrogen or fluoro.

R³ is hydrogen.

10 R³ is methyl.

R³ is hydrogen or methyl.

R³ is methyl optionally substituted by hydroxy.

R⁴ is hydrogen.

R⁴ is methyl.

15 R⁴ is methyl optionally substituted by hydroxy.

R⁴ is hydrogen or methyl.

R³ and R⁴ are hydrogen or methyl.

R⁵ is hydrogen.

R⁵ is methyl.

20 R⁵ is methyl optionally substituted by hydroxy.

R⁶ is hydrogen.

R⁶ is methyl.

R⁶ is methyl optionally substituted by hydroxy.

R⁶ is hydrogen or methyl.

25 R³ and R⁴ are both hydrogen.

R³ and R⁴ are both methyl.

R⁵ and R⁶ are both hydrogen.

R⁵ and R⁶ are both methyl.

One of R⁵ and R⁶ is methyl and the other is hydrogen or methyl.

30 One of R⁵ and R⁶ is hydrogen and the other is methyl.

Therefore is a further aspect of the invention there is provided a compound of formula

(I) wherein:

R¹ is hydrogen, fluoro, chloro or cyano;

- 5 -

R^2 is hydrogen or fluoro;

R^3 and R^4 are hydrogen or methyl;

one of R^5 and R^6 is methyl and the other is hydrogen or methyl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

5 Therefore is a further aspect of the invention there is provided a compound of formula (I) wherein:

R^1 is hydrogen, fluoro or chloro;

R^2 is hydrogen or fluoro;

R^3 and R^4 are both hydrogen or both methyl;

10 one of R^5 and R^6 is methyl and the other is hydrogen or methyl;

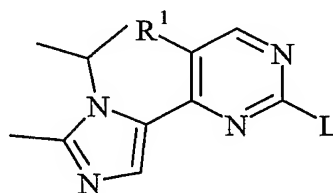
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In another aspect of the invention, preferred compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

15 Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

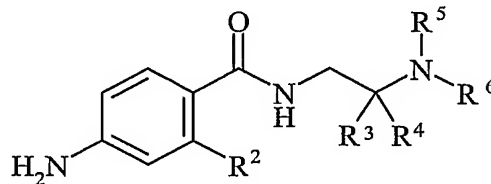
Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of:

20 *Process a)* reaction of a pyrimidine of formula (II):



(II)

wherein L is a displaceable group; with an aniline of formula (III):



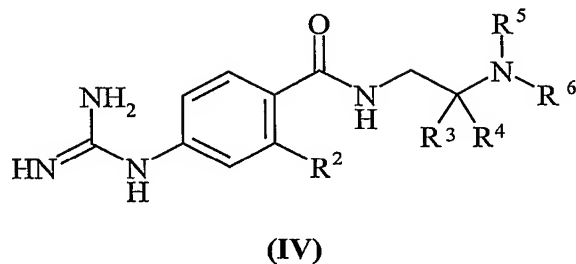
(III)

25

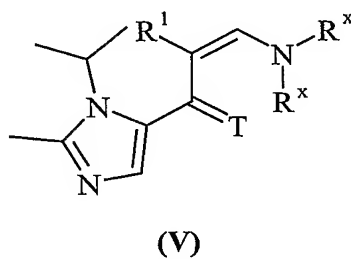
or

- 6 -

Process b) for compounds of formula (I) wherein R¹ is not cyano; reacting a compound of formula (IV):

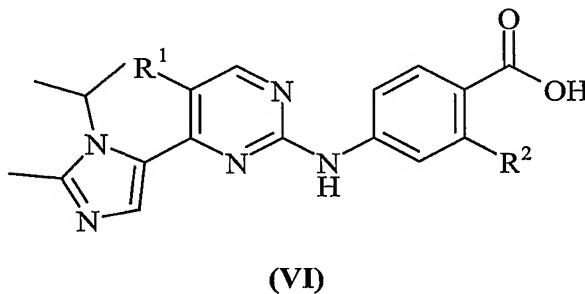


5 with a compound of formula (V):

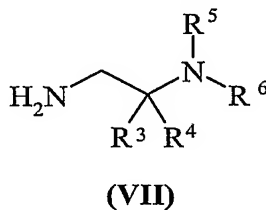


wherein T is O or S; R^x may be the same or different and is selected from C₁₋₆alkyl; or

Process c) reacting an acid of formula (VI):



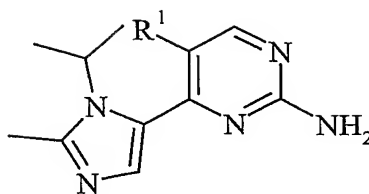
or an activated derivative thereof; with an amine of formula (VII):



15 or

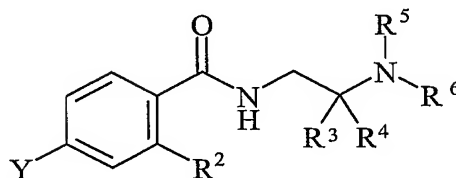
Process d) reacting a pyrimidine of formula (VIII):

- 7 -



(VIII)

with a compound of formula (IX):



(IX)

where Y is a displaceable group;

and thereafter if necessary:

- i) converting a compound of the formula (I) into another compound of the formula (I);
- ii) removing any protecting groups;
- 10 iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

- Y is a displaceable group, suitable values for Y are for example, a halogeno or
 - 15 sulphonyloxy group, for example a bromo, iodo or trifluoromethanesulphonyloxy group.
- Preferably Y is iodo.

Specific reaction conditions for the above reactions are as follows.

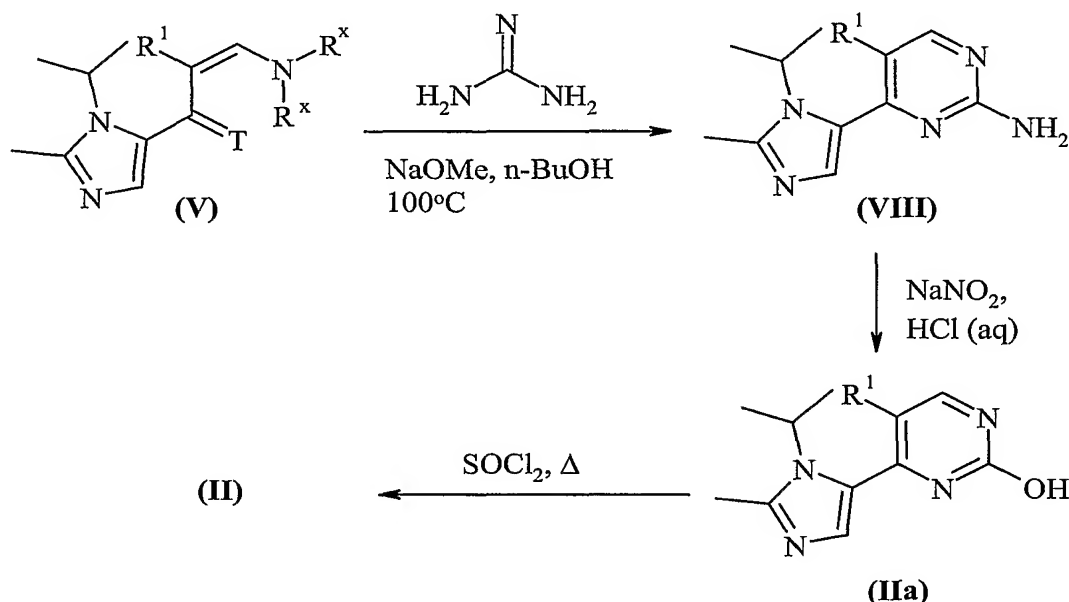
Process a) Pyrimidines of formula (II) and anilines of formula (III) may be reacted together:

- 20 i) in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolidine, optionally in the presence of a suitable acid for example an inorganic acid such as hydrochloric acid or sulphuric acid, or an organic acid such as acetic acid or formic acid (or a suitable Lewis acid) and at a temperature in the range of 0°C to reflux, preferably reflux; or
- 25 ii) under standard Buchwald conditions (for example see *J. Am. Chem. Soc.*, **118**, 7215; *J. Am. Chem. Soc.*, **119**, 8451; *J. Org. Chem.*, **62**, 1568 and 6066) for example in the presence of

- 8 -

palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium-*t*-butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and at a temperature in the range of 25 to 80°C.

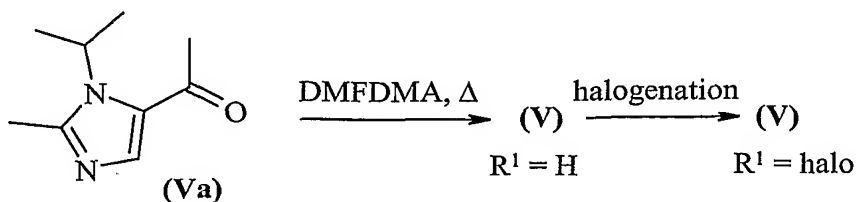
Pyrimidines of the formula (II) where L is chloro may be prepared according to Scheme 1:



Scheme 1

Anilines of formula (III) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process b) Compounds of formula (IV) and compounds of formula (V) are reacted together in a suitable solvent such as *N*-methylpyrrolidinone or butanol at a temperature in the range of 100-200°C, preferably in the range of 150-170°C. The reaction is preferably conducted in the presence of a suitable base such as, for example, sodium hydride, sodium methoxide or potassium carbonate.



Scheme 2

- 9 -

1-(1-Isopropyl-2-methyl-1*H*-imidazol-5-yl)ethanone (**Va**) is Method 3 in WO03/076436.

Compounds of formula (**IV**) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

- 5 *Process c)* Acids and amines may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for
- 10 Example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

- 15 Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

- 20 Compounds of formula (**VI**) may be prepared by adapting *Process a)* or *b)*.

Amines of formula (**VII**) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process d) Compounds of formula (**VIII**) and amines of formula (**IX**) may be reacted together under standard Buchwald conditions as described in *Process a*.

- 25 The synthesis of compounds of formula (**VIII**) is described in *Scheme 1*.

Compounds of formula (**IX**) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

- It will be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where
- 30 protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, *Protective Groups in Organic Synthesis*, John Wiley

- 10 -

and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

- 11 -

As stated hereinbefore the compounds defined in the present invention possesses anti-cell-proliferation activity such as anti-cancer activity which is believed to arise from the CDK inhibitory activity of the compound. These properties may be assessed, for example, using the procedure set out below:-

5 **Assay**

The following abbreviations have been used :-

HEPES is *N*-[2-Hydroxyethyl]piperazine-*N'*-[2-ethanesulfonic acid]

DTT is Dithiothreitol

PMSF is Phenylmethylsulphonyl fluoride

10 The compounds were tested in an *in vitro* kinase assay in 96 well format using Scintillation Proximity Assay (SPA - obtained from Amersham) for measuring incorporation of [γ -33-P]-Adenosine Triphosphate into a test substrate (GST-Retinoblastoma protein; GST-Rb). In each well was placed the compound to be tested (diluted in DMSO and water to correct concentrations) and in control wells either roscovitine as an inhibitor control or
15 DMSO as a positive control.

Approximately 0.2 μ l of CDK2/Cyclin E partially-purified enzyme (amount dependent on enzyme activity) diluted in 25 μ l incubation buffer was added to each well then 20 μ l of GST-Rb/ATP/ATP33 mixture (containing 0.5 μ g GST-Rb and 0.2 μ M ATP and 0.14 μ Ci [γ -33-P]-Adenosine Triphosphate in incubation buffer), and the resulting mixture shaken gently,
20 then incubated at room temperature for 60 minutes.

To each well was then added 150 μ L stop solution containing (0.8 mg/well of Protein A-PVT SPA bead (Amersham)), 20pM/well of Anti-Glutathione Transferase, Rabbit IgG (obtained from Molecular Probes), 61 mM EDTA and 50 mM HEPES pH 7.5 containing 0.05% sodium azide.

25 The plates were sealed with Topseal-S plate sealers, left for two hours then spun at 2500rpm, 1124xg., for 5 minutes. The plates were read on a Topcount for 30 seconds per well.

The incubation buffer used to dilute the enzyme and substrate mixes contained 50 mM HEPES pH7.5, 10 mM MnCl₂, 1 mM DTT, 100 μ M Sodium vanadate, 100 μ M NaF, 10 mM
30 Sodium Glycerophosphate, BSA (1 mg/ml final).

Test substrate

In this assay only part of the retinoblastoma protein (Science 1987 Mar13;235(4794):1394-1399; Lee W.H., Bookstein R., Hong F., Young L.J., Shew J.Y., Lee

- 12 -

E.Y.) was used, fused to a GST tag. PCR of retinoblastoma gene encoding amino acids 379-928 (obtained from retinoblastoma plasmid ATCC pLRbRNL) was performed, and the sequence cloned into pGEx 2T fusion vector (Smith D.B. and Johnson, K.S. Gene 67, 31 (1988); which contained a tac promoter for inducible expression, internal lac I^q gene for use in any E.Coli host, and a coding region for thrombin cleavage - obtained from Pharmacia Biotech) which was used to amplify amino acids 792-928. This sequence was again cloned into pGEx 2T.

The retinoblastoma 792-928 sequence so obtained was expressed in E.Coli (BL21 (DE3) pLysS cells) using standard inducible expression techniques, and purified as follows.

E.coli paste was resuspended in 10 ml/g of NETN buffer (50 mM Tris pH 7.5, 120 mM NaCl, 1 mM EDTA, 0.5%v/v NP-40, 1 mM PMSF, 1 µg/ml leupeptin, 1 µg/ml aprotinin and 1 µg/ml pepstatin) and sonicated for 2 x 45 seconds per 100 ml homogenate. After centrifugation, the supernatant was loaded onto a 10 ml glutathione Sepharose column (Pharmacia Biotech, Herts, UK), and washed with NETN buffer. After washing with kinase buffer (50 mM HEPES pH 7.5, 10 mM MgCl₂, 1 mM DTT, 1 mM PMSF, 1 µg/ml leupeptin, 1 µg/ml aprotinin and 1 µg/ml pepstatin) the protein was eluted with 50 mM reduced glutathione in kinase buffer. Fractions containing GST-Rb(792-927) were pooled and dialysed overnight against kinase buffer. The final product was analysed by Sodium Dodeca Sulfate (SDS) PAGE (Polyacrylamide gel) using 8-16% Tris-Glycine gels (Novex, San Diego, USA).

CDK2 and Cyclin E

The open reading frames of CDK2 and Cyclin E were isolated by reverse transcriptase-PCR using HeLa cell and activated T cell mRNA as a template and cloned into the insect expression vector pVL1393 (obtained from Invitrogen 1995 catalogue number: V1392-20). CDK2 and cyclin E were then dually expressed [using a standard virus Baculogold co-infection technique] in the insect SF21 cell system (Spodoptera Frugiperda cells derived from ovarian tissue of the Fall Army Worm - commercially available).

Example production of Cyclin E/CDK2

The following Example provides details of the production of Cyclin E/CDK2 in SF21 cells (in TC100 + 10% FBS(TCS) + 0.2% Pluronic) having dual infection MOI 3 for each virus of Cyclin E & CDK2.

- 13 -

SF21 cells grown in a roller bottle culture to 2.33×10^6 cells/ml were used to inoculate 10 x 500 ml roller bottles at 0.2×10^6 cells/ml. The roller bottles were incubated on a roller rig at 28°C.

After 3 days (72 hrs.) the cells were counted, and the average from 2 bottles found to be 1.86×10^6 cells/ml. (99% viable). The cultures were then infected with the dual viruses at an MOI 3 for each virus.

The viruses were mixed together before addition to the cultures, and the cultures returned to the roller rig 28°C.

After 2 days (48 hrs.) post infection the 5 Litres of culture was harvested. The total cell count at harvest was 1.58×10^6 cells/ml.(99% viable). The cells were spun out at 2500rpm, 30 mins., 4°C in Heraeus Omnifuge 2.0 RS in 250 ml. lots. The supernatant was discarded.

Partial co-purification of CDK2 and Cyclin E

Sf21 cells were resuspended in lysis buffer (50 mM Tris pH 8.2, 10 mM $MgCl_2$, 1 mM DTT, 10 mM glycerophosphate, 0.1 mM sodium orthovanadate, 0.1 mM NaF, 1 mM PMSF, 1 µg/ml leupeptin and 1 µg/ml aprotinin) and homogenised for 2 minutes in a 10 ml Dounce homogeniser. After centrifugation, the supernatant was loaded onto a Poros HQ/M 1.4/100 anion exchange column (PE Biosystems, Hertford, UK). CDK2 and Cyclin E were coeluted at the beginning of a 0-1M NaCl gradient (run in lysis buffer minus protease inhibitors) over 20 column volumes. Co-elution was checked by western blot using both anti-CDK2 and anti-Cyclin E antibodies (Santa Cruz Biotechnology, California, US).

By analogy, assays designed to assess inhibition of CDK1 and CDK4 may be constructed. CDK2 (EMBL Accession No. X62071) may be used together with Cyclin A or Cyclin E (see EMBL Accession No. M73812), and further details for such assays are contained in PCT International Publication No. WO99/21845, the relevant Biochemical & Biological Evaluation sections of which are hereby incorporated by reference.

Although the pharmacological properties of the compounds of the formula (I) vary with structural change, in general activity possessed by compounds of the formula (I) may be demonstrated at IC_{50} concentrations or doses in the range 250µM to 1nM.

When tested in the above in-vitro assay the CDK2 inhibitory activity of Example 2 was measured as $IC_{50} = 3$ nM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a pyrimidine derivative of the formula (I), or a

- 14 -

pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (I) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-80 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are effective cell cycle inhibitors (anti-cell proliferation agents), which property is believed to arise from their CDK inhibitory properties. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by CDK enzymes, i.e. the compounds may be used to produce a CDK inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for treating the proliferation of malignant cells characterised by inhibition of CDK enzymes, i.e. the compounds may be used to produce an anti-proliferative and potentially apoptotic effect mediated alone or in part by the inhibition of CDKs. Particularly, an inhibitory effect is produced by preventing entry into or progression through the S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK2 and entry into or progression through M phase by inhibition of CDK1. Apoptotic effects may also be envisaged through

- 15 -

down-regulation of RNA polymerase II activity by inhibition of CDK1, CDK7, CDK8 and in particular, CDK9. Such a compound of the invention is expected to possess a wide range of anti-cancer properties as CDKs have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach, prostate, bladder, pancreas and ovarian
5 cancer. Thus it is expected that a compound of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a compound of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth
10 of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with CDKs, especially those tumours which are significantly dependent on CDKs for their growth and spread, including for example,
15 certain tumours of the colon, breast, prostate, lung, vulva and skin.

It is further expected that a compound of the present invention will possess activity against other cell-proliferation diseases in a wide range of other disease states including leukaemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis,
20 arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use as a medicament.

25 In a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for the production of a cell cycle inhibitory effect.

In one aspect of the invention, where a cell cycle inhibitory effect is referred to this
30 refers to inhibition of CDK1. In a further aspect of the invention, this refers to inhibition of CDK2. In a further aspect of the invention, this refers to inhibition of CDK4. In a further aspect of the invention, this refers to inhibition of CDK5. In a further aspect of the invention, this refers to inhibition of CDK6. In a further aspect of the invention, this refers to inhibition

- 16 -

of CDK7. In a further aspect of the invention, this refers to inhibition of CDK8. In a further aspect of the invention, this refers to inhibition of CDK9.

In a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for the production of an anti-cell-proliferation effect.

In a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for the production of a CDK2 inhibitory effect.

In a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for the treatment of cancer.

In a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for the treatment of leukaemia or lymphoid malignancies or cancer of the breast, lung, colon, rectum, stomach, liver, kidney, prostate, bladder, pancreas, vulva, skin or ovary.

According to a further feature of the invention, there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in the manufacture of a medicament for the treatment of cancer, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

In a further aspect of the invention there is provided a method of producing a cell cycle inhibitory effect, in a warm-blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before.

In a further aspect of the invention there is provided a method of producing an anti-cell-proliferation effect, in a warm-blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I) or a

- 17 -

pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before.

In a further aspect of the invention there is provided a method of producing a CDK2 inhibitory effect, in a warm-blooded animal in need of such treatment, which comprises
5 administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before.

In a further aspect of the invention there is provided a method of treating cancer, in a warm-blooded animal in need of such treatment, which comprises administering to said
10 animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before.

In a further aspect of the invention there is provided a method of treating leukaemia or lymphoid malignancies or cancer of the breast, lung, colon, rectum, stomach, liver, kidney, prostate, bladder, pancreas, vulva, skin or ovary, in a warm-blooded animal in need of such
15 treatment, which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before.

In a further aspect of the invention there is provided a method of treating cancer, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's
20 sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, in a warm-blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined
25 herein before.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before and a pharmaceutically-acceptable diluent or carrier.

30 In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before and a pharmaceutically-acceptable diluent or carrier for use as a medicament.

- 18 -

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before and a pharmaceutically-acceptable diluent or carrier for use in the production of a cell cycle inhibitory effect.

5 In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before and a pharmaceutically-acceptable diluent or carrier for use in the production of an anti-cell-proliferation effect.

10 In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before and a pharmaceutically-acceptable diluent or carrier for use in the production of a CDK2 inhibitory effect.

15 In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before and a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancer.

20 In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before and a pharmaceutically-acceptable diluent or carrier for use in the treatment of leukaemia or lymphoid malignancies or cancer of the breast, lung, colon, rectum, stomach, liver, kidney, prostate, bladder, pancreas, vulva, skin or ovary.

25 In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before and a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancer, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

30 In a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, in the production of a cell cycle inhibitory effect.

- 19 -

In a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, in the production of an anti-cell-proliferation effect.

5 In a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, in the production of a CDK2 inhibitory effect.

In a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, in the treatment of cancer.

10 In a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the treatment of leukaemia or lymphoid malignancies or cancer of the breast, lung, colon, rectum, stomach, liver, kidney, prostate, bladder, pancreas, vulva, skin or ovary.

15 According to a further feature of the invention, there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in the treatment of cancer, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

20 Preventing cells from entering DNA synthesis by inhibition of essential S-phase initiating activities such as CDK2 initiation may also be useful in protecting normal cells of the body from toxicity of cycle-specific pharmaceutical agents. Inhibition of CDK2 or 4 will prevent progression into the cell cycle in normal cells which could limit the toxicity of cycle-specific pharmaceutical agents which act in S-phase, G2 or mitosis. Such protection may result in the prevention of hair loss normally associated with these agents.

25 Therefore in a further aspect of the invention there is provided a compound of formula (I) as defined above or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use as a cell protective agent.

30 Therefore in a further aspect of the invention there is provided a compound of formula (I) as defined above or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use in preventing hair loss arising from the treatment of malignant conditions with

- 20 -

pharmaceutical agents.

Examples of pharmaceutical agents for treating malignant conditions that are known to cause hair loss include alkylating agents such as ifosfamide and cyclophosphamide; antimetabolites such as methotrexate, 5-fluorouracil, gemcitabine and cytarabine; vinca
5 alkaloids and analogues such as vincristine, vinblastine, vindesine, vinorelbine; taxanes such as paclitaxel and docetaxel; topoisomerase I inhibitors such as irinotecan and topotecan; cytotoxic antibiotics such as doxorubicin, daunorubicin, mitoxantrone, actinomycin-D and mitomycin; and others such as etoposide and tretinoin.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically
10 acceptable salt or *in vivo* hydrolysable ester thereof, may be administered in association with a one or more of the above pharmaceutical agents. In this instance the compound of formula (I) may be administered by systemic or non systemic means. Particularly the compound of formula (I) may be administered by non-systemic means, for example topical administration.

Therefore in an additional feature of the invention, there is provided a method of
15 preventing hair loss during treatment for one or more malignant conditions with pharmaceutical agents, in a warm-blooded animal, such as man, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

In an additional feature of the invention, there is provided a method of preventing hair
20 loss during treatment for one or more malignant conditions with pharmaceutical agents, in a warm-blooded animal, such as man, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof in simultaneous, sequential or separate administration with an effective amount of said pharmaceutical agent.

25 According to a further aspect of the invention there is provided a pharmaceutical composition for use in preventing hair loss arising from the treatment of malignant conditions with pharmaceutical agents which comprises a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, and said pharmaceutical agent, in association with a pharmaceutically acceptable diluent or carrier.

30 According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, and a pharmaceutical agent for treating malignant conditions that is known to cause hair loss.

- 21 -

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, in a first unit dosage form;
- 5 b) a pharmaceutical agent for treating malignant conditions that is known to cause hair loss; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof,
10 in the manufacture of a medicament for the prevention of hair loss during treatment of malignant conditions with pharmaceutical agents.

According to a further aspect of the present invention there is provided a combination treatment for the prevention of hair loss comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo*
15 hydrolysable ester thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a pharmaceutical agent for treatment of malignant conditions to a warm-blooded animal, such as man.

As stated above the size of the dose required for the therapeutic or prophylactic
20 treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-80 mg/kg, preferably 1-50 mg/kg is envisaged.

The CDK inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or
25 treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the cell cycle inhibitory treatment defined hereinbefore may be:

30 surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

- (i) other cell cycle inhibitory agents that work by the same or different mechanisms from those defined hereinbefore;

- 22 -

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5 α -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepe); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan). According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula (I) as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer.

In addition to their use in therapeutic medicine, the compounds of formula (I) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following non limiting examples in which, unless stated otherwise:

- 5 (i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;
- (ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60°C;
- 10 (iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;
- (iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;
- (v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;
- 15 (vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;
- (vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-d₆) as solvent unless
20 otherwise indicated;
- (viii) chemical symbols have their usual meanings; SI units and symbols are used;
- (ix) solvent ratios are given in volume:volume (v/v) terms; and
- (x) mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected
25 by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is (MH)⁺;
- (xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulphur atom have not been resolved;
- 30 (xii) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;
- (xiii) the following abbreviations have been used:

- 24 -

	THF	tetrahydrofuran;
	DMF	<i>N,N</i> -dimethylformamide;
	EtOAc	ethyl acetate;
	MeOH	methanol;
5	ether	diethyl ether;
	EtOH	ethanol;
	DCM	dichloromethane;
	DMSO	dimethylsulphoxide;
	DIAD	diisopropyl azodicarboxylate;
10	TEA	triethylamine;
	HBTU	<i>O</i> -benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate;
	DIPEA	<i>N,N</i> -diisopropylethylamine;
	MPLC	medium pressure liquid chromatography;
15	RPHPLC	reverse phase high performance liquid chromatography; and
	Xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene;

(xiv) where an SCX-2 column is referred to, this means an "ion exchange" extraction cartridge for adsorption of basic compounds, i.e. a polypropylene tube containing a benzenesulphonic acid based strong cation exchange sorbent, used according to the
 20 manufacturers instructions obtained from International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ.

Example 1

N-(2-Dimethylaminoethyl)-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide
 25

4-(3-Isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine (Method 1; 0.15 g), palladium acetate (10 mg), Xantphos (48 mg), caesium carbonate (0.45 g) and N-(2-dimethylaminoethyl)-4-iodo-benzamide (Method 4; 0.24 g) were added to dioxane (9 ml) under an inert atmosphere and heated at reflux for 9 hrs. The reaction mixture was then
 30 concentrated *in vacuo*, the residue loaded onto a SCX-2 column in MeOH, washed with MeOH then eluted with 7N NH₃ in MeOH. Further purification was achieved using RPHPLC to give the title compound (0.212 g); NMR (400.132 MHz, CDCl₃) 8.38 (d, 1H), 7.80 (d, 2H),

- 25 -

7.68 (d, 2H), 7.38 (s, 1H), 7.22 (s, 1H), 6.96 (d, 1H), 6.83 (brs, 1H), 5.65 (septet, 1H), 3.54 (q, 2H), 2.60 (s, 3H), 2.57 (t, 2H), 2.31 (s, 6H), 1.55 (d, 6H); m/z 408.

Example 2

5 N-(2-Dimethylaminoethyl)-2-fluoro-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using 4-bromo-N-(2-dimethylaminoethyl)-2-fluoro-benzamide (Method 5) and 4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine (Method 1); NMR (400.132
10 MHz, CDCl₃) 8.40 (d, 1H), 8.04 (t, 1H), 7.80 (dd, 1H), 7.53 (s, 1H), 7.40 (s, 1H), 7.24 (dd, 1H), 7.00 (d, 1H), 5.64 (septet, 1H), 3.56 (q, 2H), 2.60 (s, 3H), 2.53 (t, 3H), 2.29 (s, 6H), 1.56 (d, 6H); m/z 426.

Example 3

15 N-(2-Dimethylaminoethyl)-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using N-(2-dimethylaminoethyl)-4-iodo-benzamide (Method 4) and 5-fluoro-4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine (Method 3). NMR (400.132
20 MHz, CDCl₃) 8.31 (d, 1H), 7.78 (d, 2H), 7.63 (d, 2H), 7.59 (d, 1H), 7.22 (s, 1H), 6.78 - 6.72 (brs, 1H), 5.57 (septet, 1H), 3.52 (q, 2H), 2.62 (s, 3H), 2.52 (t, 2H), 2.28 (s, 6H), 1.54 (d, 6H); m/z 426.

Example 4

25 N-(2-Dimethylaminoethyl)-2-fluoro-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using 4-bromo-N-(2-dimethylaminoethyl)-2-fluoro-benzamide (Method 5) and 5-fluoro-4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine (Method 3). NMR
30 (400.132 MHz, CDCl₃) 8.33 (d, 1H), 8.04 (t, 1H), 7.73 (dd, 1H), 7.61 (d, 1H), 7.34 (s, 1H), 7.21 - 7.15 (m, 2H), 5.55 (septet, 1H), 3.56 (q, 2H), 2.63 (s, 3H), 2.52 (t, 2H), 2.28 (s, 6H), 1.56 (d, 6H); m/z 444.

- 26 -

Example 5

4-[[5-Chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-dimethylaminoethyl)-2-fluoro-benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using 4-bromo-N-(2-dimethylaminoethyl)-2-fluoro-benzamide (Method 5) and 5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-amine (Method 5 in WO05/075461). NMR (400.132 MHz, CDCl₃) 8.48 (s, 1H), 8.03 (t, 1H), 7.77 (dd, 1H), 7.68 (s, 1H), 7.53 (s, 1H), 7.24 - 7.19 (m, 2H), 4.95 (septet, 1H), 3.56 (q, 2H), 2.61 (s, 3H), 2.54 (t, 2H), 2.29 (s, 6H), 1.50 (d, 6H); m/z 460.

Example 6

N-(2-Methylaminoethyl)-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using 4-iodo-N-(2-methylaminoethyl)benzamide (Method 6) and 4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine (Method 1). NMR (400.132 MHz, CDCl₃) 8.36 (d, 1H), 7.81 (d, 2H), 7.66 (d, 2H), 7.41 (s, 1H), 7.37 (s, 1H), 7.00 (t, 1H), 6.95 (d, 1H), 5.64 (septet, 1H), 3.59 (q, 2H), 2.90 (t, 2H), 2.58 (s, 3H), 2.50 (s, 3H), 1.53 (d, 6H); m/z 394.

Example 7

4-[[5-Fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-methylaminoethyl)benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using 4-iodo-N-(2-methylaminoethyl)benzamide (Method 6) and 5-fluoro-4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine (Method 3). NMR (400.132 MHz, CDCl₃) 8.30 (d, 1H), 7.79 (d, 2H), 7.62 (d, 2H), 7.59 (d, 1H), 7.34 (s, 1H), 6.79 (s, 1H), 5.57 (septet, 1H), 3.55 (q, 2H), 2.84 (t, 2H), 2.61 (s, 3H), 2.46 (s, 3H), 1.83 - 1.68 (m, 1H), 1.53 (d, 6H); m/z 412.

- 27 -

Example 8

4-[[5-Chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-methylaminoethyl)benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using 4-iodo-N-(2-methylaminoethyl)benzamide (Method 6) and 5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-amine (Method 5 in WO05/075461). NMR (400.132 MHz, CDCl₃) 8.45 (s, 1H), 7.78 (d, 2H), 7.63 (d, 2H), 7.52 (s, 1H), 7.44 (s, 1H), 6.80 (s, 1H), 4.95 (septet, 1H), 3.55 (q, 2H), 2.84 (t, 2H), 2.59 (s, 3H), 2.46 (s, 3H), 1.48 (d, 6H); m/z 428.

Example 9

4-[[5-Chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-2-fluoro-N-(2-methylaminoethyl)benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using 4-bromo-2-fluoro-N-(2-methylaminoethyl)benzamide (Method 7) and 5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-amine (Method 5 in WO05/075461). NMR (400.132 MHz, CDCl₃) 8.49 (s, 1H), 8.05 (t, 1H), 7.78 (dd, 1H), 7.54 (s, 1H), 7.41 (s, 1H), 7.19 (dd, 1H), 7.12 - 7.09 (m, 1H), 4.96 (septet, 1H), 3.58 (q, 2H), 2.84 (t, 2H), 2.61 (s, 3H), 2.47 (s, 3H), 1.51 (d, 6H); m/z 446.

Example 10

2-Fluoro-N-(2-methylaminoethyl)-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using 4-bromo-2-fluoro-N-(2-methylaminoethyl)benzamide (Method 7) and 4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine (Method 1). NMR (400.132 MHz, CDCl₃) 8.40 (d, 1H), 8.03 (t, 1H), 7.91 (s, 1H), 7.81 (d, 1H), 7.39 (s, 1H), 7.24 (d, 1H), 7.14 - 7.11 (m, 1H), 7.00 (d, 1H), 5.64 (septet, 1H), 3.59 (q, 2H), 2.84 (t, 2H), 2.60 (s, 3H), 2.47 (s, 3H), 1.55 (d, 6H); 412.

Example 11

2-Fluoro-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-methylaminoethyl)benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using 4-bromo-2-fluoro-N-(2-methylaminoethyl)benzamide (Method 7) and 5-fluoro-4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine (Method 3). NMR (400.132 MHz, CDCl₃) 8.33 (d, 1H), 8.07 - 8.01 (m, 1H), 7.74 (d of d, 1H), 7.60 (d, 1H), 7.48 (s, 1H), 7.20 (d of d, 1H), 7.14 - 7.07 (m, 1H), 5.56 (septet, 1H), 3.58 (q, 2H), 2.84 (t, 2H), 2.63 (s, 3H), 2.47 (s, 3H), 1.56 (d, 6H); m/z 430.

Example 12

N-(2-Dimethylamino-2-methyl-propyl)-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide

4-[[5-Fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino} benzoic acid lithium salt (Method 9) (0.2 g) and HBTU (0.25 g) were dissolved in DMF (5 ml). N,N,2-trimethylpropane-1,2-diamine (0.07 g) was then added followed by DIPEA (0.21 ml) and the reaction mixture was stirred for 16 hrs. The solvent was then removed *in vacuo* and the residue was passed through a SCX-2 column, eluting with MeOH and then with 3.5N NH₃ in MeOH. The solid obtained was recrystallised from a mixture of acetonitrile / ether to give the title compound as a colourless solid (0.05 g). NMR (400.132 MHz, CDCl₃) 8.30 (d, 1H), 7.79 (d, 2H), 7.65 - 7.58 (m, 3H), 7.18 (s, 1H), 6.95 - 6.91 (m, 1H), 5.56 (septet, 1H), 3.35 (d, 2H), 2.62 (s, 3H), 2.24 (s, 6H), 1.54 (d, 6H), 1.08 (s, 6H); m/z 455.

Example 13

N-(2-Dimethylamino-2-methyl-propyl)-2-fluoro-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide

The title compound was prepared by the procedure of Example 12 and on the same scale, using 2-fluoro-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzoic acid lithium salt (Method 11) and N,N,2-trimethylpropane-1,2-diamine. NMR (400.132 MHz, CDCl₃) 8.33 (d, 1H), 8.03 (t, 1H), 7.72 (dd, 1H), 7.60 (d, 1H), 7.45 - 7.37 (m, 1H), 7.27 (s, 1H), 7.20 (dd, 1H), 5.55 (septet, 1H), 3.39 (d, 2H), 2.63 (s, 3H), 2.24 (s, 6H), 1.56 (d, 6H), 1.07 (s, 6H); m/z 472.

Example 14

N-(2-Dimethylamino-2-methyl-propyl)-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide

The title compound was prepared by the procedure of Example 12 and on the same scale, using 4-{[4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino} benzoic acid lithium salt (Method 13) and N,N,2-trimethylpropane-1,2-diamine. Purification was by RPHPLC instead of recrystallization. NMR (400.132 MHz, CDCl₃) 8.37 (d, 1H), 7.82 - 7.77 (m, 2H), 7.71 - 7.67 (m, 3H), 7.38 (s, 1H), 7.00 - 6.96 (m, 1H), 6.95 (d, 1H), 5.66 (septet, 1H), 3.36 (d, 2H), 2.59 (s, 3H), 2.24 (s, 6H), 1.53 (d, 6H), 1.07 (s, 6H); m/z 437.

Example 15

N-(2-Dimethylamino-2-methyl-propyl)-2-fluoro-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide

The title compound was prepared by the procedure of Example 12 and on the same scale, using 2-fluoro-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzoic acid sodium salt (Method 15) and N,N,2-trimethylpropane-1,2-diamine. Purification was by RPHPLC instead of recrystallization. NMR (400.132 MHz, CDCl₃) 8.40 (d, 1H), 8.03 (t, 1H), 7.79 (dd, 1H), 7.45 - 7.37 (m, 2H), 7.32 (s, 1H), 7.24 (dd, 1H), 7.00 (d, 1H), 5.63 (septet, 1H), 3.39 (d, H), 2.60 (s, 3H), 2.24 (s, 6H), 1.56 (d, 6H), 1.07 (s, 6H); m/z 455.

Example 16

4-[[5-Chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-dimethylamino-2-methyl-propyl)benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using N-(2-dimethylamino-2-methyl-propyl)-4-iodo-benzamide (Method 16) and 5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-amine (Method 5 in WO05/075461). NMR (400.132 MHz, CDCl₃) 8.45 (s, 1H), 7.78 (d, 2H), 7.65 (d, 2H), 7.52 (s, 1H), 7.36 (s, 1H), 6.93 (s, 1H), 4.94 (septet, 1H), 3.35 (d, 2H), 2.60 (s, 3H), 2.24 (s, 6H), 1.49 (d, 6H), 1.07 (s, 6H); m/z 471.

- 30 -

Example 17

4-[[5-Chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-dimethylaminoethyl)benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using N-(2-dimethylaminoethyl)-4-iodo-benzamide (Method 4) and 5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-amine (Method 5 in WO05/075461). NMR (400.132 MHz, CDCl₃) 8.45 (s, 1H), 7.79 (d, 2H), 7.64 (d, 2H), 7.58 (s, 1H), 7.51 (s, 1H), 6.90 (s, 1H), 4.94 (septet, 1H), 3.53 (q, 2H), 2.59 (s, 3H), 2.53 (t, 2H), 2.28 (s, 6H), 1.48 (d, 6H); m/z 443.

Example 18

4-[[5-Chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-dimethylamino-2-methyl-propyl)-2-fluoro-benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using 4-bromo-N-(2-dimethylamino-2-methyl-propyl)-2-fluoro-benzamide (Method 17) and 5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-amine (Method 5 in WO05/075461). NMR (399.902 MHz, CDCl₃) 8.48 (s, 1H), 8.03 (t, 1H), 7.76 (dd, 1H), 7.54 (s, 1H), 7.45 - 7.35 (m, 2H), 7.20 (dd, 1H), 4.95 (septet, 1H), 3.39 (d, 2H), 2.61 (s, 3H), 2.24 (s, 6H), 1.51 (d, 6H), 1.07 (s, 6H); m/z 489.

Example 19

4-[[5-Chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-2-fluoro-N-[(2S)-2-methylaminopropyl]benzamide

N-Methyl-2,4-dinitro-benzenesulfonamide (in Example 274 in WO01/000206; 288 mg, 1.1 mmol) and triphenylphosphine (315 mg, 1.2 mmol) were added to a stirred solution of 4-[[5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-2-fluoro-N-[(2R)-2-hydroxypropyl]benzamide (Method 19, 446 mg, 1.0 mmol) in THF (15 ml) under an inert atmosphere. DIAD (243 mg, 1.2 mmol) was then added dropwise, the solution stirred for 30 mins before adding additional triphenylphosphine (315 mg, 1.2 mmol) and DIAD (243 mg, 1.2 mmol). After stirring for 30 mins the solvent was evaporated and the residue purified on silica by MPLC (Gilson, 40 g cartridge), eluting with 5% MeOH / DCM to give a mixture of two products. The mixture was dissolved in DCM (10 ml) and n-propylamine (1 ml) was added, after 30 minutes the reaction mixture was evaporated and the residue dissolved in

- 31 -

EtOAc. The organic layer was washed with aq. ammonia, dried (MgSO₄), filtered and concentrated to give a gum. Purification on silica by MPLC (Gilson, 40 g cartridge) eluting with 1% to 10% NH₃-MeOH / DCM followed by crystallisation with ether gave the title compound as a colourless solid (37 mg, 8%). NMR (399.9 MHz) 10.23 (s, 1H), 8.72 (s, 1H), 7.87 (q, 1H), 7.79-7.75 (m, 1H), 7.65 (t, 1H), 7.53-7.50 (m, 1H), 7.28 (s, 1H), 4.86-4.79 (m, 1H), 3.27-3.22 (m, 1H), 3.20-3.16 (m, 1H), 2.68 (q, 1H), 2.50 (s, 3H), 2.30 (s, 3H), 2.00 (bs, 1H), 1.49-1.39 (m, 6H), 0.99 (d, 3H); m/z 461.

Example 20

4-[[5-Chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-2-fluoro-N-[(2R)-2-methylaminopropyl]benzamide

The title compound was prepared by the procedure of Example 19 and on the same scale, using 4-[[5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-2-fluoro-N-[(2S)-2-hydroxypropyl]benzamide (Method 21). NMR (399.9 MHz) 10.23 (s, 1H), 8.72 (s, 1H), 7.87 (q, 1H), 7.79-7.75 (m, 1H), 7.65 (t, 1H), 7.53-7.50 (m, 1H), 7.28 (s, 1H), 4.86-4.79 (m, 1H), 3.27-3.22 (m, 1H), 3.20-3.16 (m, 1H), 2.68 (q, 1H), 2.50 (s, 3H), 2.30 (s, 3H), 2.00 (bs, 1H), 1.49-1.39 (m, 6H), 0.99 (d, 3H); m/z 461.

Example 21

4-[[5-Cyano-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-dimethylaminoethyl)-2-fluoro-benzamide

The title compound was prepared by the procedure of Example 1 and on the same scale, using 4-bromo-N-(2-dimethylaminoethyl)-2-fluoro-benzamide (Method 5) and 2-amino-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidine-5-carbonitrile (Method 23).

NMR (400.132 MHz, CDCl₃) 8.70 (s, 1H), 8.09 - 8.05 (m, 2H), 7.85 (s, 1H), 7.74 (d, 1H), 7.30 - 7.27 (m, 1H), 7.25 - 7.22 (m, 1H), 5.23 (septet, 1H), 3.56 (q, 2H), 2.62 (s, 3H), 2.53 (t, 2H), 2.28 (s, 6H), 1.53 (d, 6H); m/z 451.

Preparation of Starting materials

Method 1

4-(3-Isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine

(2*E*)-3-(Dimethylamino)-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one, (Method 24 of WO 03/076436 4.0 g, 18 mmol) and guanidine carbonate (7.2 g, 40 mmol) were pre-mixed in 2-methoxyethanol (80 ml) and heated at reflux for 30 hours. The reaction was allowed to cool before being quenched with water (50 ml). The reaction was then extracted with DCM (2 x 200 ml), dried and solvent was removed *in vacuo* to yield a yellow solid. The solid was dissolved in minimum amount of warm DCM, this was then allowed to cool before the addition of ether. An off white solid precipitated this was filtered and dried. The process was repeated to obtain second crop of product (3.18 g, 81%). NMR (299.954 MHz, CDCl₃): 8.22 (d, 1H), 7.33 (s, 1H), 6.80 (d, 1H), 5.45 (septet, 1H), 5.10 (s, 2H), 2.56 (s, 3H), 1.54 (d, 6H); m/z 218.

Method 2

(2*Z*)-3-(Dimethylamino)-2-fluoro-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one

To a stirred solution of (2*E*)-3-(dimethylamino)-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one, (Method 24 of WO 03/076436; 5.53 g, 25 mmol) in MeOH (100 ml) at ambient temperature was added in portions over ~5 mins (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (14.16 g, 40 mmol). The temperature was maintained at 25-30°C by slight cooling. After stirring for 90 mins the reaction mixture was cooled in ice/acetone and filtered. The filtrate was evaporated under reduced pressure and the residue was taken into DCM. It was washed with aq. ammonia, brine, dried (Na₂SO₄) and evaporated under reduced pressure. The title compound was isolated by MPLC on silica gel using two separate columns (10% EtOH / EtOAc, then 3.5% EtOH / DCM) as a golden viscose oil, which crystallized on standing over several weeks. Yield = 2.50 g (42%). NMR: 1.40 (d, 6H), 2.38 (s, 3H), 3.05 (s, 6H), 4.70 (septet, 1H), 6.96 (d, 1H), 7.08 (s, 1H); fluorine NMR (376MHz): -166.7 (d); m/z 240.

- 33 -

Method 3**5-Fluoro-4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine**

(2*Z*)-3-(Dimethylamino)-2-fluoro-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 2; 4.0 g, 16.7 mmol) and guanidine carbonate (6.6 g, 37 mmol) were pre-mixed in butanol (80 ml) and heated at reflux for 30 hours. The reaction was allowed to cool before being quenched with water (200 ml) the reaction was then extracted with DCM (2 x 200 ml), dried and solvent was removed *in vacuo* to yield a yellow solid. The solid was dissolved in minimum amount of warm DCM, this was then allowed to cool before the addition of ether. An off white solid precipitated this was filtered and dried. The process was repeated to obtain second crop of product (3.18 g, 81%). NMR (299.954 MHz, CDCl₃): 8.15 (d, 1H), 7.54 (d, 1H), 7.26 (s, 1H), 5.40 (septet, 1H), 4.88 (s, 2H), 2.59 (s, 3H), 1.56 (d, 6H); m/z 236.

Method 4**N-(2-Dimethylaminoethyl)-4-iodo-benzamide**

N,N-Dimethylethylenediamine (2 g) was added to a stirred solution of 4-iodobenzoyl chloride (5 g) and TEA (3.9 ml) in DCM (150 ml) under an inert atmosphere. After 1 hr 2M NaOH (50 ml) was added and the mixture extracted with DCM (3 x 100 ml). The combined organics were dried and concentrated *in vacuo* to give the title compound as a brown gum which solidified on standing (4.7 g). NMR (400.132 MHz, CDCl₃) 7.77 (d, 2H), 7.51 (d, 2H), 6.78 (brs, 1H), 3.50 (q, 2H), 2.51 (t, 2H), 2.27 (s, 6H); m/z 319.

Method 5**4-Bromo-N-(2-dimethylaminoethyl)-2-fluoro-benzamide**

4-Bromo-2-fluorobenzoic acid (5 g), and HBTU (9.5 g) were dissolved in DMF (150 ml), and then N,N-dimethylethylenediamine (2.1 g) and DIPEA (10.3 ml) were added. The reaction was stirred for 24 hrs before the removal of the DMF *in vacuo*, the gum was quenched with 2.0M NaOH (50 ml), extracted with DCM (3 x 200 ml), dried and the solvent removed *in vacuo* to yield a viscous gum. Purification by distillation (145°C at 1.2 mmBar) gave the title compound as a yellow gum (5.8 g). NMR (400.132 MHz, CDCl₃) 7.96 (t, 1H), 7.40 (dd, 1H), 7.30 (dd, 1H), 7.20 (brs, 1H), 3.53 (q, 2H), 2.51 (t, 2H), 2.27 (s, 6H); m/z 290.

- 34 -

Method 6**4-Iodo-N-(2-methylaminoethyl)benzamide**

tert-Butyl N-(2-aminoethyl)-N-methyl-carbamate (4.16 g) was added to a stirred solution of 4-iodobenzoyl chloride (6.4 g) and TEA (6.2 ml) in DCM (150 ml) under an inert atmosphere. After 20 mins satd. aq. NH₄Cl (50 ml) was added and the mixture was extracted with DCM (3 x 100 ml). The combined organics were dried and concentrated *in vacuo* to give a yellow gum (9.0 g), which was dissolved in acetonitrile (30 ml). 6.0M HCl in propan-2-ol was added and the reaction mixture was stirred overnight. The precipitated solid was filtered and dried to give the title compound as an off-white solid (5.2 g). NMR (400.132 MHz) 9.08 - 8.89 (m, 2H), 7.87 (d, 2H), 7.72 (d, 2H), 3.57 (q, 2H), 3.12 - 3.06 (m, 2H), 2.58 - 2.56 (m, 3H); m/z 305.

Method 7**4-Bromo-2-fluoro-N-(2-methylaminoethyl)benzamide**

4-Bromo-2-fluorobenzoic acid (8.2 g), and HBTU (18.4 g) were dissolved in DMF (100 ml), and then tert-butyl N-(2-aminoethyl)-N-methyl-carbamate (6.5 g) and DIPEA (13.3 ml) were added. The reaction was stirred for 24 hrs before adding 2M NaOH (50 ml) then extracting with DCM (3 x 100 ml). The combined organics were dried, filtered and concentrated *in vacuo* to give a yellow gum that was dissolved in MeCN (30 ml). 6M HCl in propan-2-ol was added, the reaction mixture stirred for 24 hrs before filtering and drying to give the title compound as an off-white solid (7.4 g). NMR (400.132 MHz) 9.19 - 9.00 (m, 2H), 8.65 (s, 1H), 7.72 (t, 1H), 7.67 (dd, 1H), 7.53 (dd, 1H), 3.58 (q, 2H), 3.32 (s, 3H), 3.10 - 3.03 (m, 2H); m/z 276.

Method 8**Ethyl 4-{{[5-fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}benzoate**

To a solution of 5-fluoro-4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine (Method 3; 5.32 g) in dioxane (100 ml) was added ethyl 4-iodobenzoate (3.59 g), palladium (II) acetate (305 mg), Xantphos (1.18 g), and caesium carbonate (14.74 g). The mixture was degassed, and purged with nitrogen, then heated at reflux for 3 hrs. The mixture was cooled to ambient temperature, the solids removed by filtration, then the filtrate concentrated *in vacuo*. Purification on silica using 2-5 % MeOH in DCM as eluent gave the

- 35 -

title compound as a yellow solid (2.75 g, 32%). NMR 9.97 (s, 1H), 8.62 (d, 1H), 7.88 (d, 2H), 7.80 (d, 2H), 7.38 (d, 1H), 5.47 - 5.38 (m, 1H), 4.27 (q, 2H), 2.53 (s, 3H), 1.46 (d, 6H), 1.30 (t, 3H); m/z 384.

5 Method 9

4-{[5-Fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}benzoic acid lithium salt

To a stirred solution of ethyl 4-{[5-fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}benzoate (Method 8; 2.75 g) in EtOH (70 ml) was added a solution
10 of lithium hydroxide (301 mg) in water (15 ml). The mixture was heated under reflux for 18 hrs, then concentrated in vacuo and partitioned between water (300 ml) and EtOAc (300 ml). The aqueous layer was washed with further EtOAc (200 ml) then concentrated in vacuo to yield the title compound as a white solid (2.07 g). NMR 9.56 (s, 1H), 8.53 (d, 1H), 7.80 (d, 2H), 7.53 (d, 2H), 7.36 (d, 1H), 5.56 - 5.46 (m, 1H), 2.51 (s, 3H), 1.43 (d, 6H); m/z 356.

15

Method 10

Ethyl 2-fluoro-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzoate

The title compound was prepared in similar manner to Method 8 using ethyl 4-bromo-
20 2-fluoro-benzoate in place of ethyl 4-iodobenzoate and purification was achieved by trituration with DCM to give the title compound as a brown solid (3.2 g). NMR (400 MHz) 10.28-10.09 (br s, 1H), 8.68 (d, 1H), 7.87-7.77 (m, 2H), 7.51 (dd, 1H), 7.40 (d, 1H), 5.47-5.34 (m, 1H), 4.29 (q, 2H), 2.55 (s, 3H), 1.48 (d, 6H), 1.30 (t, 3H); m/z 402.

25 Method 11

2-Fluoro-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzoic acid lithium salt

The title compound was prepared in similar manner to Method 9 from ethyl 2-fluoro-
4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzoate
30 (Method 10) in place of ethyl 4-{[5-fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}benzoate (Method 8). NMR (400 MHz) 9.68 (br s, 1H), 8.58 (d, 1H), 7.57 (t, 1H), 7.44 (dd, 1H), 7.37 (d, 1H), 7.26 (dd, 1H), 5.54-5.42 (m, 1H), 2.53 (s, 3H), 1.46 (d, 6H); m/z 374.

- 36 -

Method 12**Ethyl 4-{[4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}benzoate**

To a solution of 4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine (Method 1; 7.8 g) in dioxane (200 ml) was added ethyl 4-iodobenzoate (9.445 g), palladium (II) acetate (461 mg), Xantphos (1.785 g), and caesium carbonate (22.29 g). The mixture was degassed, and purged with nitrogen, then heated at reflux for 3 hrs. The mixture was cooled to ambient temperature, the solids removed by filtration, and then the filtrate was concentrated in vacuo. Purification on silica using 2-5 % MeOH in DCM as eluent gave the title compound as a yellow solid (3.82 g, 31%). NMR 9.87 (s, 1H), 8.46 (d, 1H), 7.90 - 7.83 (m, 4H), 7.45 (s, 1H), 7.14 (d, 1H), 5.72 - 5.63 (m, 1H), 4.27 (q, 2H), 2.49 (s, 3H), 1.47 (d, 6H), 1.30 (t, 3H); m/z 366.

Method 13**4-{[4-(1-Isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}benzoic acid lithium salt**

The title compound was prepared in similar manner to Method 9 from ethyl 4-{[4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}benzoate (Method 12) in place of ethyl 4-{[5-fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}benzoate (Method 8). NMR (400.132 MHz) 9.51 (s, 1H), 8.40 (d, 1H), 7.85 (d, 2H), 7.61 (d, 2H), 7.43 (s, 1H), 7.05 (d, 1H), 5.78 (m, 1H), 2.50 (s, 3H), 1.45 (d, 6H); m/z 338.

Method 14**Methyl 2-fluoro-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzoate**

The title compound was prepared in similar manner to Method 9 using methyl 4-bromo-2-fluoro-benzoate in place of ethyl 4-iodobenzoate to give the title compound as a colourless oil (2.27 g). NMR: 10.08 (s, 1H), 8.50 (d, 1H), 7.92-7.76 (m, 2H), 7.54 (d, 1H), 7.46 (s, 1H), 7.19 (d, 1H), 5.72-5.58 (m, 1H), 3.80 (s, 3H), 2.50 (s, 3H under DMSO), 1.48 (d, 6H); m/z 370.

Method 15**2-Fluoro-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzoic acid sodium salt**

- Methyl 2-fluoro-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzoate (Method 14; 1.27 g) was dissolved in THF (10 ml) and 1N NaOH was added (3.5 ml). The mixture was heated at reflux for 16 hrs. The reaction mixture was cooled to ambient temperature and the solvent evaporated *in vacuo*. The solid residue was triturated with MeOH then filtered and dried to give a colourless solid (0.8 g). The filtrate was concentrated and triturated with EtOAc, filtered and dried to give a second batch (0.92 g). The two batches were combined to give the title compound as a colourless solid (1.72 g); NMR 400MHz) 9.56 (s, 1H), 8.42 (d, 2H), 7.56 (t, 1H), 7.48 (dd, 1H), 7.44 (s, 1H), 7.24 (dd, 1H), 7.08 (d, 1H), 5.80-5.68 (m, 1H), 2.50 (s, 3H under DMSO), 1.47 (d, 6H); m/z 356.

Method 16**N-(2-Dimethylamino-2-methyl-propyl)-4-iodo-benzamide**

- The title compound was prepared by the procedure of Method 4, using N,N-2-trimethylpropane-1,2-diamine in place of N,N-dimethylethylenediamine and purification was by trituration from MeCN/ DCM to give a colourless solid. NMR (400.132 MHz, CDCl₃) 7.78 (d, 2H), 7.52 (d, 2H), 6.95 (brs, 1H), 3.33 (d, 2H), 2.23 (s, 6H), 1.06 (s, 6H); m/z 347.

Method 17**4-Bromo-N-(2-dimethylamino-2-methyl-propyl)-2-fluoro-benzamide**

- The title compound was prepared by the procedure of Method 18, using N,N-2-trimethylpropane-1,2-diamine in place of (2R)-1-aminopropan-2-ol. Purification was by MPLC to give the title compound as colourless oil. NMR (399.902 MHz, CDCl₃) 7.94 (t, 1H), 7.46 (br s, 1H), 7.40 (dd, 1H), 7.31 (dd, 1H), 3.38 (d, 2H), 2.24 (s, 6H), 1.07 (s, 6H); m/z 318.

Method 18**4-Bromo-2-fluoro-N-[(2R)-2-hydroxypropyl]benzamide**

- 4-Bromo-2-fluoro-benzoyl chloride (4.75 g, 20 mmol) was added dropwise to a stirred solution of (2R)-1-aminopropan-2-ol (1.81 g, 24 mmol) and triethylamine (3.03 g, 30 mmol) in DCM (75 ml) at 0-4°C. The solution was warmed to ambient temperature, stirred for 30

- 38 -

mins then washed with 2N HCl, water and sat NaHCO₃. The solvent was evaporated to give a crystalline mass which was triturated with ether / hexane to give the title compound (4.83 g, 88%). NMR (399.9 MHz, CDCl₃) 7.97 (t, 1H), 7.43-7.41 (m, 1H), 7.35-7.31 (m, 1H), 7.05 (s, 1H), 4.08-4.03 (m, 1H), 3.70-3.64 (m, 1H), 3.38-3.31 (m, 1H), 2.30 (d, 1H), 1.26 (d, 3H); m/z 277.

Method 19

4-[[5-Chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-2-fluoro-N-[(2R)-2-hydroxypropyl]benzamide

The title compound was prepared by the procedure of Example 1, using 4-bromo-2-fluoro-N-[(2R)-2-hydroxypropyl]benzamide (Method 18) and 5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-amine (Method 5 in WO05/075461). NMR (399.9 MHz) 10.23 (s, 1H), 8.72 (s, 1H), 7.83 (q, 1H), 7.80-7.76 (m, 1H), 7.67 (t, 1H), 7.52-7.49 (m, 1H), 7.28 (s, 1H), 4.87-4.80 (m, 1H), 4.76-4.75 (m, 1H), 3.81-3.75 (m, 1H), 3.28-3.23 (m, 1H), 3.21-3.18 (m, 1H), 2.50 (s, 3H), 1.43 (d, 6H), 1.08 (d, 3H); m/z 448.

Method 20

4-Bromo-2-fluoro-N-[(2S)-2-hydroxypropyl]benzamide

The title compound was prepared by the procedure of Method 18, using (2S)-1-aminopropan-2-ol in place of (2R)-1-aminopropan-2-ol. NMR (399.9 MHz, CDCl₃) 7.97 (t, 1H), 7.43-7.41 (m, 1H), 7.35-7.31 (m, 1H), 7.05 (s, 1H), 4.08-4.03 (m, 1H), 3.70-3.64 (m, 1H), 3.38-3.31 (m, 1H), 2.30 (d, 1H), 1.26 (d, 3H); m/z 277.

Method 21

4-[[5-Chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-2-fluoro-N-[(2S)-2-hydroxypropyl]benzamide

The title compound was prepared by the procedure of Example 1, using 4-bromo-2-fluoro-N-[(2S)-2-hydroxypropyl]benzamide (Method 20) and 5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-amine (Method 5 in WO05/075461). NMR (399.9 MHz) 10.23 (s, 1H), 8.72 (s, 1H), 7.83 (q, 1H), 7.80-7.76 (m, 1H), 7.67 (t, 1H), 7.52-7.49 (m, 1H), 7.28 (s, 1H), 4.87-4.80 (m, 1H), 4.76-4.75 (m, 1H), 3.81-3.75 (m, 1H), 3.28-3.23 (m, 1H), 3.21-3.18 (m, 1H), 2.50 (s, 3H), 1.43 (d, 6H), 1.08 (d, 3H); m/z 448.

- 39 -

Method 22**5-Iodo-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-amine**

A solution of 4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamine (Method 1, 3 g, 13.8 mmol) and N-iodosuccinimide (3.3 g, 14.5 mmol) in acetic acid (35 ml) was heated at 50°C for 16 hrs. The reaction was evaporated, quenched with aq. sodium thiosulphate until colourless and then 2.0 M NaOH (50 ml) was added. The aqueous layer was extracted with DCM (3 x 200 ml), the combined organics were dried (MgSO₄) and the solvent evaporated to give a colourless solid. The solid was added to acetonitrile, heated to 60°C and then allowed to cool before being filtered, the process was repeated on the filtrate to give the title compound as a colourless solid (3.5 g, 74%). NMR (400.132 MHz, CDCl₃) 8.62 (s, 1H), 7.34 (s, 1H), 5.08 (br s, 2H), 4.57 (septet, 1H), 2.55 (s, 3H), 1.48 (d, 6H); m/z 344.

Method 23**2-Amino-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidine-5-carbonitrile**

A solution of 5-iodo-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-amine (Method 22, 2.2 g, 6.4 mmol) and CuCN (2.2 g, 12.8 mmol) in pyridine (60 ml) was heated under reflux for 2 days. The solvent was evaporated, the residue was dissolved in DMF and loaded onto a SCX column (50 g), washing with DMF and MeOH then eluting with 7M ammonia/ MeOH. The residue obtained was dissolved in DCM, then 2.0 M NaOH (100 ml) was added and the aqueous layer extracted with additional DCM (3 x 200 ml). The combined organics were dried and the solvent evaporated to give a yellow solid, which was dissolved in the minimum amount of hot acetonitrile, cooled and filtered. The process was repeated with the filtrate to give the title compound as an off-white solid (0.81 g, 52%). NMR (400.132 MHz, CDCl₃) 8.54 (s, 1H), 7.79 (s, 1H), 5.60 (brs, 2H), 5.11 (septet, 1H), 2.59 (s, 3H), 1.55 (d, 6H); m/z 243.

Example 22

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

- 40 -

(a): Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c): Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d): Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

- 41 -

(e): Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f): Injection II	10 mg/ml
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

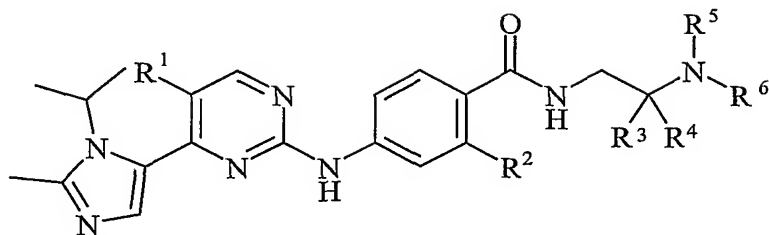
(g): Injection III	(1 mg/ml,buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

Claims

1. A compound of formula (I):



(I)

wherein:

R¹ is hydrogen, halo or cyano;

R² is hydrogen or halo;

R³, R⁴, R⁵ and R⁶ are independently selected from hydrogen and methyl optionally substituted by hydroxy;
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

2. A compound of formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, as claimed in claim 1 wherein R¹ is hydrogen, fluoro, chloro or cyano.

3. A compound of formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, as claimed in either claim 1 or claim 2 wherein R² is hydrogen or fluoro.

4. A compound of formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-3 wherein R³ is hydrogen or methyl.

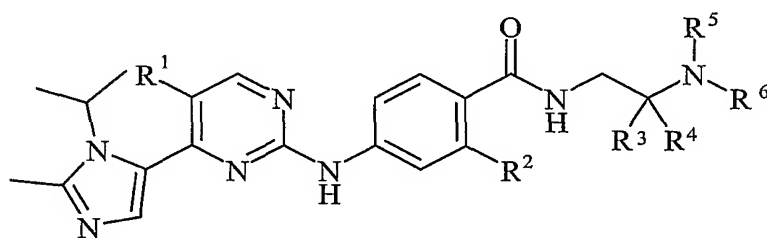
5. A compound of formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-4 wherein R⁴ is hydrogen or methyl.

- 43 -

6. A compound of formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-5 wherein R⁵ is methyl.

7. A compound of formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-6 wherein R⁶ is hydrogen or methyl.

8. A compound of formula (I):



10

(I)

wherein:

R¹ is hydrogen, fluoro, chloro or cyano;

R² is hydrogen or fluoro;

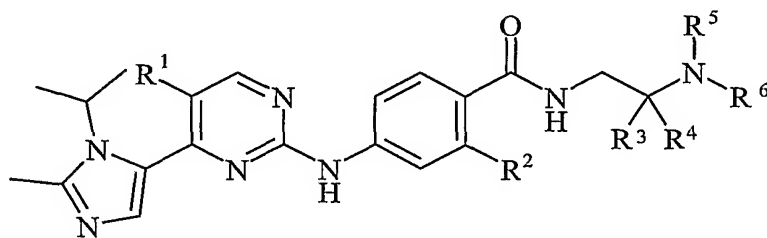
R³ and R⁴ are hydrogen or methyl;

15

one of R⁵ and R⁶ is methyl and the other is hydrogen or methyl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

9. A compound of formula (I):



20

(I)

selected from:

N-(2-dimethylaminoethyl)-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide;

- 44 -

N-(2-dimethylaminoethyl)-2-fluoro-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide;

N-(2-dimethylaminoethyl)-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide;

5 N-(2-dimethylaminoethyl)-2-fluoro-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide;

4-[[5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-dimethylaminoethyl)-2-fluoro-benzamide;

N-(2-methylaminoethyl)-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide;

10 4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-methylaminoethyl)benzamide;

4-[[5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-methylaminoethyl)benzamide;

15 4-[[5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-2-fluoro-N-(2-methylaminoethyl)benzamide;

2-fluoro-N-(2-methylaminoethyl)-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide;

20 2-fluoro-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-methylaminoethyl)benzamide;

N-(2-dimethylamino-2-methyl-propyl)-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide;

N-(2-dimethylamino-2-methyl-propyl)-2-fluoro-4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide;

25 N-(2-dimethylamino-2-methyl-propyl)-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide;

N-(2-dimethylamino-2-methyl-propyl)-2-fluoro-4-[[4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]benzamide;

4-[[5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-dimethylamino-2-methyl-propyl)benzamide;

30 4-[[5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-dimethylaminoethyl)benzamide;

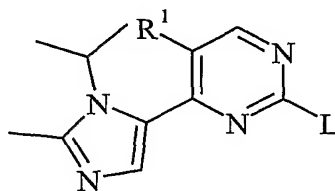
- 45 -

4-[[5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-dimethylamino-2-methyl-propyl)-2-fluoro-benzamide;
 4-[[5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-2-fluoro-N-[(2S)-2-methylaminopropyl]benzamide;
 5 4-[[5-chloro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-2-fluoro-N-[(2R)-2-methylaminopropyl]benzamide; and
 4-[[5-cyano-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]-N-(2-dimethylaminoethyl)-2-fluoro-benzamide;
 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

10

10. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, as claimed in claim 1, which process comprises of:

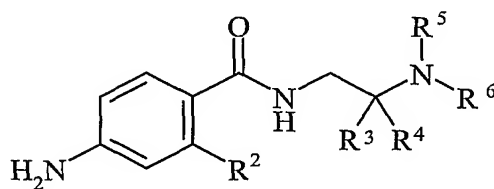
Process a) reaction of a pyrimidine of formula (II):



15

(II)

wherein L is a displaceable group; with an aniline of formula (III):

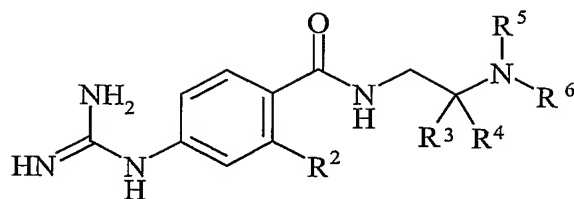


(III)

20 or

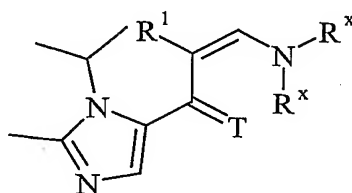
Process b) for compounds of formula (I) wherein R¹ is not cyano; reacting a compound of formula (IV):

- 46 -



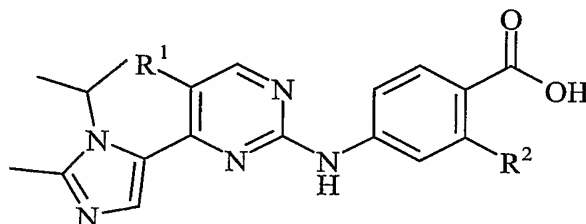
(IV)

with a compound of formula (V):



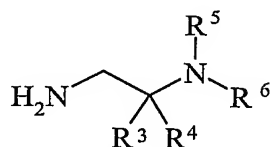
(V)

wherein T is O or S; R^x may be the same or different and is selected from C₁₋₆alkyl; or
Process c) reacting an acid of formula (VI):



(VI)

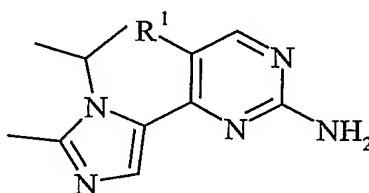
or an activated derivative thereof; with an amine of formula (VII):



(VII)

or

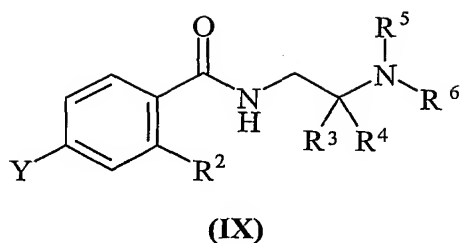
Process d) reacting a pyrimidine of formula (VIII):



(VIII)

- 47 -

with a compound of formula (IX):



where Y is a displaceable group;

5 and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

10 11. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-9, and a pharmaceutically-acceptable diluent or carrier.

12. A compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo*
 15 hydrolysable ester thereof, as claimed in any one of claims 1-9, for use as a medicament.

13. The use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-9, in the manufacture of a medicament for the production of an anti-cell-proliferation effect.

20

14. The use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-9, in the manufacture of a medicament in the production of a CDK2 inhibitory effect.

25 15. The use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-9, in the manufacture of a medicament for the treatment of cancer.

16. The use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-9, in the manufacture of a
 30

- 48 -

medicament for the treatment of leukaemia or lymphoid malignancies or cancer of the breast, lung, colon, rectum, stomach, liver, kidney, prostate, bladder, pancreas, vulva, skin or ovary.

17. The use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-9, in the manufacture of a medicament for the treatment of cancer, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

18. A method of producing an anti-cell-proliferation effect, in a warm-blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-9.

19. A method of producing a CDK2 inhibitory effect, in a warm-blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-9.

20. A method of treating cancer, in a warm-blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-9.

21. A method of treating leukaemia or lymphoid malignancies or cancer of the breast, lung, colon, rectum, stomach, liver, kidney, prostate, bladder, pancreas, vulva, skin or ovary, in a warm-blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-9.

22. A method of treating cancer, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies,

- 49 -

atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, in a warm-blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-9.

5

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2007/002279

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/04 A61P35/02 A61P35/04 A61K31/506

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/075461 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; ANDREWS DAVID MICHAEL [G]) 18 August 2005 (2005-08-18) -----	1-22
A	WO 02/20512 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BREAUULT GLORIA ANNE [GB]) 14 March 2002 (2002-03-14) cited in the application -----	1-22

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

23 August 2007

Date of mailing of the international search report

30/08/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Tabanella, Stefania

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2007/002279

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2007/002279

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005075461 A	18-08-2005	AR 047702 A1	08-02-2006
		AU 2005210248 A1	18-08-2005
		BR PI0507351 A	03-07-2007
		CA 2554076 A1	18-08-2005
		EP 1748999 A1	07-02-2007
		KR 20060129040 A	14-12-2006
		US 2007161615 A1	12-07-2007
WO 0220512 A1	14-03-2002	AT 269327 T	15-07-2004
		AU 8419201 A	22-03-2002
		BG 107579 A	31-10-2003
		BR 0113496 A	01-07-2003
		CA 2417148 A1	14-03-2002
		CN 1452620 A	29-10-2003
		CZ 20030617 A3	18-06-2003
		DE 60103935 D1	22-07-2004
		DE 60103935 T2	21-07-2005
		DK 1351958 T3	06-09-2004
		EE 200300088 A	15-02-2005
		EP 1351958 A1	15-10-2003
		ES 2221904 T3	16-01-2005
		HK 1057553 A1	31-12-2004
		HU 0302922 A2	29-12-2003
		IS 6715 A	12-02-2003
		JP 3523641 B2	26-04-2004
		JP 2004508365 T	18-03-2004
		MX PA03001511 A	09-06-2003
		NO 20031006 A	04-03-2003
		NZ 523787 A	24-09-2004
		PL 360627 A1	20-09-2004
		PT 1351958 T	30-09-2004
		RU 2284327 C2	27-09-2006
		SK 2412003 A3	11-09-2003
		TW 242559 B	01-11-2005
		US 2006004033 A1	05-01-2006
		US 2004014776 A1	22-01-2004
		ZA 200300612 A	22-04-2004